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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/284,009	LEWIS ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *05 April 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☒ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

[illegible]

15)☐ Notice of [illegible]

17)☒ Information Disclosure Statements (PTO-[illegible]) Paper No(s). 3

20)☐ Other: [illegible]

DETAILED ACTION

Priority

1. This application filed on April 05, 1999, is a 371 of PCT/GB97/02709 and claims priority to 3 applications filed in Great Britain (9620952.3, 9701975.6, and 97,03670.1) dated 10/09/96, 01/30/97 and 02/21/97 respectively.

Claims

2. Claims 1-24 will be considered in this office action.

3. Preliminary amendment dated April 5, 1999 is acknowledged.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-18 and 21-24, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a 'therapeutic composition' comprising a (i) regulatable agent and (ii) an agent that binds to a cell surface element of a mononuclear phagocyte and (iii) a therapeutic gene incorporated into the nucleus of the phagocyte.

'Therapeutic composition' reads broadly on a composition that on being administered, ameliorates the symptoms of a disease thus inducing therapy.

The specification teaches in-vitro infiltration of macrophages into tissue biopsies, and taught that a direct correlation exists between macrophage infiltration and tumor angiogenesis. In vitro experiments have also been performed using a adenoviral vector comprising a lacZ gene under the control of a hypoxia regulated promoter-enhancer.

The specification describes the preparation of a retroviral vector, and its transfer to monocyte cell line U937 cells, but does not teach stepwise as to how this is to be used for therapy.

They also experimented with nude mice into which human breast cancer xenografts had been grown and the effect of hypoxia on macrophage infiltration. Nude mice have an immune system that is non-functional. The immune system of non-nude mice would normally be activated when a virus in introduced, rejecting the virus. Hence the use of nude mice is not an appropriate model for this study. J. Gomez-Navarro et al. in their review article on Gene Therapy for Cancer in 1999, stated that one obstacle that needs to be overcome for curing cancer is the development of better animal models including tumor models in transgenic mice. Hence the results of this study could not be extrapolated to be used for human gene therapy. In addition, details as to therapeutic dosages, length of time the administration of the said vector has to be used to elicit a sustained shrinkage of tumors etc. are lacking.

Neither does, the specification teach any invivo or exvivo therapy for reduction of tissue tumors by reduction of the infiltration of macrophages to the site of the tumor. Therefore, no working examples have been provided to demonstrate therapy.

The state of the art in gene therapy is still in its infancy and is highly unpredictable. "Clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol" (see Orkin et al. Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, distributed by the National Institutes of Health, Bethesda, MD or www. nih.gov, page 1).

Gene therapy aims to alleviate or cure diseases by altering the genetic makeup of the individual. The first clinical trials for genetic therapy were conducted in 1990. However, there is still no single outcome to point to as a success story after hundreds of clinical trials have been performed worldwide on thousands of individuals. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 2). The major problems that have been encountered are (1) the delivery of the altered genes, and (2) the inability to obtain a sustained expression of the desired protein in a specified location. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 5).

Being a new field the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and induce a therapeutic response. Hence the specification requires detailed methods for preparation of the therapeutic compositions comprising the adenoviral vector, ligand

and/or gene, including specific dosages for specific therapies, as claimed by the inventions. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

6. Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is only enabling for *in-vitro* applications, which demonstrate that the macrophage concentration in areas of stress (for instance a tumor), is high. The specification does not provide enablement for the selective destroying of mononuclear phagocytes *in-vitro*. Neither does the specification provide enablement for *in-vivo* or *ex-vivo* applications which demonstrate that a high macrophage concentration is seen in tumors. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 19 and 20 recite methods of destroying phagocytes. There are however no results given which indicate that phagocytes were destroyed by any of the professed methods for example by cytotoxic genes introduced via an adenoviral vector.

Due to the factors discussed above, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy. Since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 19 is rejected under 35 U.S.C. 112, second paragraph as it is vague and indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 19 contains the term 'optionally'. This term is misleading as it is unclear as to whether the agent needs to bind to the mononuclear phagocyte or not. The claim

needs to be amended to reflect the applicant's intention with regards to the specific limitations of the claim.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferkol, Jr. et al.(patent # 5,972,900) in view of Ratcliffe et al. (patent # 5,942,434), and further in view of Leek et al.

The claims recite a composition comprising a regulatable agent and an agent that binds to a cell surface element, wherein the regulatable agent could be either hypoxia, ischemia, or stress regulatable agent comprising a therapeutic gene, wherein the binding agent could be a ligand which could be mannosylated poly-L-lysine.

Ferkol et al. taught that receptor-mediated gene transfer has been shown to be successful in introducing transgenes into cells *in-vitro*. They taught that this procedure involved linking the DNA to a polycationic protein usually poly-L-lysine containing a covalently attached ligand, which is selected to target a specific receptor on the surface of the tissue of interest. (See col. 1 lines 25-30). Ferkol et al. also taught the tissue specificity of mannosylated DNA complex in targeting DNA to macrophages, which are

Ferkol et al. did not teach that the inclusion of a regulatable agent that could be a hypoxia, ischemia, or stress regulatable agent or a therapeutic gene.

Ratcliffe et al. taught that nucleic acid constructs comprising hypoxia response elements in linkage with a coding sequence of a gene of interest which could encode prodrug activation systems or cytokines, and taught *in-vitro* methods for the same. Ratcliffe also taught that several vectors including retinoviral vectors could be used as mechanism for delivery. (See col. 4 line 45). These experiments were conducted in order to measure hypoxically-induced expression of genes. (See Abstract, claims and col, 9 lines 10-15).

At the time of the invention, the prevalent thinking was that monocytes enter a tumor and differentiate into macrophages, which preferentially congregate in hypoxic sites deep within the tumor mass far from blood vessels (See specification page 2 lines 17-20) and Leek et al.(see pg. 4626, col. 1, para. 5). Hence, applicants would have been motivated to combine the teachings of Ferkol et al. with that of Ratcliffe, to result in the instant invention.

Therefore it would have been *prima facie* obvious at the time the invention was made to combine the teachings of Ferkol, Ratcliffe and Leek to make nucleic acid constructs comprising hypoxia responsive elements for delivery into specific cells. Therefore one of ordinary skill in the art would have been motivated to modify the non-targeting constructs, responsive to hypoxia responsive elements and include a specific ligand or sequence, enabling it to target a specific cell type. The aspect of delivering

known in the art and does not require undue experimentation. One of ordinary skill in the art would have reasonably expected success because the field of molecular biology is relatively advanced in that modifying constructs with sequences that fulfill a desired end result would not require undue experimentation.

Conclusion

10. Claims 1-24 are rejected.

11. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.